a potassium channel agonist of a calcium-activated or ATP-sensitive potassium channel, said potassium channel agonist being other than bradykinin or a bradykinin analog; and

instructions for using the potassium channel agonist for enhancing the delivery of a medicant to an abnormal brain region by increasing the permeability of a capillary or arteriole delivering blood to cells of the abnormal brain region.

Please add new Claims 110-112.

--110. (New) The method of Claim 1, wherein the medicant is a DNA expression vector, viral vector, oligonucleotide, or nucleotide analog.

111. (New) The method of Claim 18, wherein the medicant is a DNA expression vector, viral vector, oligonucleotide, or nucleotide analog.

112. (New) The pharmaceutical composition of Claim 97, wherein the medicant is a DNA expression vector, viral vector, oligonucleotide, or nucleotide analog.--.

REMARKS

Pending Claims

Prior to the above amendments, Claims 1-34 and 97-109 are pending. Claims 1-34 are directed to a method of delivering a medicant to an abnormal brain region in a mammalian subject. Claims 97-107 relate to a pharmaceutical composition. Claims 108-109 are directed to a kit for enhancing the delivery of a medicant to an abnormal brain region and/or to a malignant tumor.

The Office Action, Applicant's Amendment, and Summary of Telephonic Interview (March 14, 2001)

In the Office Action, no claims were allowed.

Examiner Nikodem acknowledged Applicant's previous Response to Office Action, which Applicant mailed September 20, 2000, and the amendments therein.

Examiner Nikodem maintained the rejections of Claims 1-34 and 97-109 under 35 U.S.C. § 103 over Black (U.S. Patent No. 5,434,137), in combination with Sobey *et al.* (Stroke 28[11]:2290-4 [1997]) and Cherksey (U.S. Patent No. 5,234,947).

The rejection of Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34 for obviousness type double patenting was maintained in view of Black (U.S. Patent No. 5,434,137), in combination with Sobey *et al.* (Stroke 28[11]:2290-4 [1997]) and Cherksey (U.S. Patent No. 5,234,947).

Claims 1-34 and 97-109 were further rejected under 35 U.S.C. § 112, first paragraph.

On March 14, 2001, Examiner Eleanor Sorbello and Supervisory Examiner Deborah Clark graciously granted Applicant's undersigned attorney a telephonic interview with the participation of the inventors, Dr. Keith L. Black, Director of the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai Medical Center, and Dr. Nagendra S. Ningaraj, Research Scientist, Maxine Dunitz Neurosurgical Institute.

In the interview, Applicant's undersigned attorney stated that Applicant desired to address the Examiner's rejections perhaps more clearly than Applicant was able to do in the Response to Office Action, mailed September 20, 2000, and that it was not clear from the pending Office Action that Examiner Nikodem had considered, along with Applicant's arguments, the supporting references (Exhibits A-F), which Applicant had attached to the Response to Office Action, mailed September 20, 2000. In reply, Examiner Clark stated that Examiner Nikodem should have properly addressed in particular each reference brought by Applicant in the context of Applicant's responsive arguments.

Then, Dr. Black clarified the four main types of potassium channels: inverse rectifier potassium channels (K_{ir}); voltage-gated potassium channels (K_v); calcium-activated potassium channels (K_{Ca}); and ATP-sensitive potassium channels (K_{ATP}). Applicant then proposed the

voluntary amendment of Claims 1, 97, and 108 to clarify that the potassium channel agonist is "of a calcium-activated or ATP-sensitive potassium channel, said potassium channel agonist being other than bradykinin or a bradykinin analog . . ." Applicant herein also voluntarily amends claim 18 in this way, as well as Claims 1, 97, and 108, for greater clarity as to the metes and bounds of the invention. Applicant emphasizes that these amendments are not made in response to any issues of patentability concerning the prior art of record. Support for these amendments is found in the specification, for example, at page 10, lines 14-16.

In addition, the Examiners suggested during the interview an amendment of Claim 108 to recite "by increasing the permeability of a capillary or arteriole delivering blood to cells of the abnormal brain region." Applicant has so amended Claim 108.

The Examiners also stated late in the interview that the recitation in Claim 6 of "wherein the medicant is a . . . DNA expression vector, viral vector, . . . oligonucleotide, [or] nucleotide analog" lacks enablement due to the unpredictability of the art. Merely to facilitate allowance of Claims 6, 23, and 101, Applicant has deleted from the Markush groups of those claims the recitation of "DNA expression vector", "viral vector", "oligonucleotide", and "nucleotide analog" and has placed them in new Claims 110-112. In support of new Claims 110-112, Applicant herein presents references that show that DNA expression vectors, viral vectors, oligonucleotides, or nucleotide analogs were known treatment modalities or "medicants", at the time the specification was originally filed.

In particular, expression vectors and viral vectors had been used in human clinical trials and in vivo animal models for the treatment of brain cancer and other neurological disorders affecting the central nervous system. (E.g., Shand, N. *et al.*, *A phase 1-2 clinical trial of gene therapy for recurrent glioblastoma multiforme by tumor transduction with the herpes simplex thymidine kinase gene followed by gancylovir. GLI328 European-Canadian Study Group*, Hum. Gene Ther. 10(14):2325-35 [1999], abstract appended as Exhibit G; Hlavety, J. *et al.*, *Cells producing recombinant retrovirus with thymidine kinase gene from Herpes simplex virus suitable for human cancer gene therapy*, Neoplasma 46(6):329-34 [1999], abstract appended as Exhibit H; Jacobs, A. *et al.*, *HSV-1-based vectors for gene therapy of neurological diseases and brain tumors: Part II. vector systems and applications*, Neoplasia

1(5):402-16 [1999], abstract appended as Exhibit I; Marconi, P. *et al.*, *Connexin 43-enhanced suicide gene therapy using herpesviral vectors*, Mol. Ther. 1(1):71-81 [Jan. 2000], abstract appended as Exhibit J).

Antisense oligonucleotides were also known for treating brain cancers, at least in animal models, in vivo. (E.g., Im, S.A., *et al.*, *Antiangiogenesis tretment for gliomas: transfer of anti-sense-vascular endothelial growth factor inhibits tumor growth in vivo*, Cancer Res. 59(4):895-900 [1999], abstract appended as Exhibit K; Yazaki, T. *et al.*, *Treatment of glioblastoma U-87 by systemic administration of an antisense protein kinase C-alpha phosphorothioate oligodeoxynucleotide*, Mol. Pharmacol. 50(2):236-42 [1996], abstract appended as Exhibit L).

Nucleotide analogs, such as 5-fluorocytosine, were also known as medicants for treating brain tumors . (E.g., Adachi, Y. *et al.*, *Experimental gene therapy for brain tumors using adenovirus-mediated transfer of cytosine deaminase gene and uracil phosphoribosyltransferase with 5-fluorocytosine*, Hum. Gene Ther. 11(1):77-89 [Jan.1, 2000], abstract appended as Exhibit M).

In addition, Applicant has deleted "anticancer chemotherapeutic agent" from Claims 6 and 23, as being directed to the subject matter of a non-elected group, as Applicant previously amended Claim 101 in Applicant's Response to Office Action, mailed September 20, 2000.

During the course of the telephonic interview, Applicant's undersigned attorney addressed in detail the following grounds of rejection presented in the pending Office Action, which the Examiners requested Applicant to submit in the form of this written Response to Office Action.

A.1. Rejection of Claims 1-34 and 97-109 under 35 U.S.C. § 103(a)

During the telephonic interview, Applicant made three main arguments against this ground of rejection: (1) Vasodilators are not per se associated in the art as agents that increase Blood Brain Barrier permeability; (2) Bradykinin and its analogs are in a distinct class of compounds and are chemically unlike other K_{Ca} and K_{ATP} agonists; and (3) Sobey *et al.* taught

the vasodilation effect of bradykinin in *normal* brain microvascular, and none of the cited references suggested the relatively greater quantity of potassium channels in abnormal brain microvasculature compared to normal microvasculature, as taught by Applicant's specification.

(1) Vasodilators are not per se associated in the art as agents that increase Blood Brain Barrier permeability

Claims 1-34 and 97-109 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Black (U.S. Patent No. 5,434,137), in view of the combination of Sobey *et al.* (Stroke 28[11]:2290-4 [1997]) and Cherksey (U.S. Patent No. 5,234,947). Examiner Nikodem had stated, in relevant part, that "Sobey *et al.* teaches that vasodilator responses of cerebral arterioles to bradykinin involve the activation of potassium channels. This is direct evidence that bradykinin is an agonist of potassium channels and increases ion flux and potassium ion concentrations." (Office Action, Item 4). He further stated, ". . . Although Black does not teach the mechanism of bradykinin, the prior art reference Sobey *et al.* does," and he added, ". . . Black further teaches bradykinin increases the permeability of the blood brain barrier in abnormal tissue. This is a direct link between the two mechanisms of bradykinin . . ." (Office Action, Items 5 and 6).

While Sobey *et al.* taught the involvement of calcium-activated potassium channels in the vasodilatation of normal brain capillaries by bradykinin, they failed to describe any effect on microvascular permeability. Contrary to Examiner's assertion, Sobey *et al.*'s teaching of a mechanism for vasodilatation failed to make obvious to the skilled artisan the claimed method of delivering a medicant to an abnormal brain region, because it was known in the art that the process of vasodilatation is independent of microvascular permeability. Vasodilators are not per se associated in the art as agents that increase Blood Brain Barrier permeability.

Examiner Clark asked why, in light of the cited Black patent, it would not have been obvious that a vasodilator, such as bradykinin, would also increase microvascular permeability. As Dr. Black replied, the skilled artisan would have been aware of references that negate a mechanistic linkage between vasodilatation and microvascular permeability. For example, leukotriene C4 (LTC4) is a known *vasoconstrictor*. (See, e.g., Yakubu, M. A. *et al.*, *Hematoma-*

induced enhanced cerebral vasoconstrictions to leukotriene C4 and endothelin-1 in piglets: role of prostanoids, Pediatr. Res 38(1):119-23 [1995], abstract appended as Exhibit A; and Black *et al.*, *Selective opening of the blood-tumor barrier by intracarotid infusion of leukotriene C4*, J. Neurosurg. 72:912-16 [1990], appended as Exhibit B). Yet it was shown that LTC4 could increase microvascular permeability in abnormal brain tissue (gliomas implanted in rat brains; Exhibit B). This result taught away from a conclusion that vasodilatation is involved in microvascular permeability.

Also, the skilled artisan was aware that other known pathways, clearly unrelated to vasodilatation, affected microvascular permeability. For example, a number of calcium channel antagonists, such as nifedipine, that are not known to increase vasodilatation of cerebral microvessels had been shown to increase the permeability of abnormal brain capillaries. (See, Matsukado *et al.*, *Selective increase in blood-tumor barrier permeability by calcium antagonists in transplanted rat brain tumors*, Acta Neurochir. Suppl. (Wien) 60:403-05 [1994], abstract appended as Exhibit C). This result also taught away from a conclusion that vasodilatation is involved in microvascular permeability.

The potassium channel activators of Cherksey were useful for treating hypertension, addiction, asthma, incontinence, and other conditions presumably related to vascular hypertension. (See, e.g., Abstract; column 4, lines 6-27). Like Sobey *et al.*, the teachings of Cherksey relate to a mechanism of vasorelaxation, i.e., vasodilatation. Cherksey taught that the opening of vascular plasmalemmal potassium (K^+) channels produces loss of cytosolic K^+, resulting in "cellular hyperpolarization and functional vasorelaxation." (Column 3, line 59 through column 4, line 5; emphasis added), but Cherksey failed to teach any connection with microvascular permeability.

Therefore, Cherksey, like Sobey *et al.*, in combination with the cited Black patent, failed to make obvious the claimed method that relies on increasing microvascular permeability in abnormal microvasculature.

(2) Bradykinin and its analogs are in a distinct class of compounds and are chemically unlike other K_{Ca} and K_{ATP} agonists

Examiner Nikodem stated, in relevant part, that ". . . [i]n view of the effect of bradykinin disclosed in Black and the teachings of Sobey *et al.* to the mechanism of bradykinin and the teaching a multitude of other bradykinin-like agonists by Cherksey, one of skill in the art would have expected some degree of success by other potassium channel agonists." (Office Action, Item 7). The Examiner also stated, ". . . [i]t would have been obvious for one of skill in the art to investigate other potassium channel agonists, similar to bradykinin, in order to determine if a similar effect is seen-namely that of increasing potassium ion flux and potassium ion concentrations in abnormal brain vasculature." (Office Action, Item 5).

Applicant strongly disagrees. In describing the use of bradykinin and its analogs, Sobey *et al.* combined with Black failed to make obvious "administering to a mammalian subject having an abnormal brain region a potassium channel agonist of a calcium-activated or ATP-sensitive potassium channel . . . other than bradykinin or a bradykinin analog", because bradykinin and its analogs are in a distinct chemical class, of short peptides. For example, the specification as originally filed describes bradykinin and its analogs:

> [T] he potassium channel agonist employed in the inventive methods is one other than the vasodilator bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), or a polypeptide bradykinin analog, such as receptor mediated permeabilizer (RMP)-7 or A7 (e.g., Kozarich et al., U.S. Patent No. 5,268,164 and PCT Application No. WO 92/18529). Other analogs of bradykinin include related peptide structures which exhibit the same properties as bradykinin but have modified amino acids or peptide extensions on either terminal end of the peptide. Examples of bradykinin analogs include [phe.sup.8 (CH.sub.2 –NH) Arg.sup.9]-bradykinin, N–acetyl [phe.sup.8 (CH.sub.2 --NH--Arg.sup.9] bradykinin and desArg9-bradykinin. (Specification, at page 11, lines 4-11).

Bradykinin is an endogenously produced pro-inflammatory nonapeptide that has chemical properties distinct from other K_{Ca} and K_{ATP} activators, such as those exemplified in the specification, e.g., at page 10, line 14 through page 11, line 3. Also, Cherksey described a structurally distinct class of chemicals with potassium channel-activating properties, which,

contrary to the Examiner's assertion, are not "bradykinin-like", but rather chemically distinct from bradykinin and its analogs (see, Cherksey, Abstract; and column 4, lines 6-45).

Beyond its distinct chemical structure, other chemical properties of bradykinin are clearly distinct. For example, vasodilatation mediated by bradykinin, an agonist of K_{Ca}, was shown to be mediated by a different process from vasodilatation mediated by some agonists of K_{ATP}, such as prostacyclin or cromakalim. For example, bradykinin-mediated vasodilatation, which is nitric oxide synthase (NOS)-mediated (Liu, Q. and Flavahan N.A., *Hypoxic dilatation of porcine small coronary arteries: role of endothelium and KATP-channels*, Br. J. Pharmacol. 120(4):728-34 [1997], abstract appended as Exhibit E), was not inhibited by glibenclamide, a specific inhibitor of ATP-sensitive potassium channels, unless a nitric oxide synthase inhibitor was also present, while vasodilatation mediated by prostacyclin or cromakalim was shown to be inhibited directly by glibenclamide. (See, e.g., Jackson, W.F. *et al.*, *Prostacyclin-induced vasodilatation in rabbit heart is mediated by ATP-sensitive potassium channels*, Am. J. Physiol. 264(1 Pt 2):H238-43 [1993], abstract appended as Exhibit D). Conversely, inhibitors of bradykinin-mediated vasodilatation, such as L-NAME or L-NNA, were shown not to inhibit vasodilatation mediated by cromakalim. (Liu, Q. and Flavahan N.A., *Hypoxic dilatation of porcine small coronary arteries: role of endothelium and KATP-channels*, Br. J. Pharmacol. 120(4):728-34 [1997], abstract Exhibit E; and Herrera, G.M. *et al.*, *Maintained vasodilatory response to cromakalim after inhibition of nitric oxide sysnthesis*, J. Cardiovasc. Pharmacol. 31(6):921-29 [1998], abstract appended as Exhibit F). Therefore, the mechanism of vasodilatory action of bradykinin was and is thought to be independent of the vasodilatory pathway mediated by some ATP-sensitive potassium channels. This is only one example showing different chemical properties of bradykinin compared to other potassium channel activators.

Thus, the examiner's assertion that "it would have been obvious for one of skill in the art to investigate other potassium channel agonists, *similar to bradykinin*" does not address the claimed invention that relates to administering a "potassium channel agonist of a calcium-activated or ATP-sensitive potassium channel, said potassium channel agonist being *other than bradykinin or a bradykinin analog*." And as to K_{Ca} and K_{ATP} activators other than bradykinin or a bradykinin analog, i.e., those chemically distinct from bradykinin and its analogs, Examiner

Nikodem appears to have made an improper "obvious to try" argument, which is not the legal standard of obviousness. (E.g., *In re Goodwin*, 198 USPQ 1, 3 [CCPA 1978]; *In re Geiger*, 2 USPQ2d 1276, 1278 [Fed. Cir. 1987]).

Consequently, without the hindsight provided by Applicant's specification, success would not have been reasonably expected for the claimed method that employs an agonist of either calcium-activated potassium channels or ATP-sensitive potassium channels, as recited, e.g., in Claim18 or in accordance with amended Claim 1.

(3) Sobey *et al.* taught the vasodilation effect of bradykinin in normal brain microvascular, and none of the cited references suggested the relatively greater quantity of potassium channels in abnormal brain microvasculature compared to normal microvasculature, as taught by Applicant's specification.

As Dr. Black pointed out during the telephonic interview, Sobey *et al.* studied the vasodlatory effect of bradykinin in normal rat cerebral arterioles. Thus, even if Sobey *et al.* had *arguendo* described a mechanism for increasing microvascular permeability in normal microvessels, they would have failed to describe or suggest a mechanism by which abnormal microvasculature, i.e., capillaries and arterioles delivering blood to the cells of an abnormal brain region, can be made selectively more permeable to a medicant compared to the microvasculature of normal brain regions, so that the "medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions", as required, for example, in Claim 1 and 18.

In contrast, Example 2 of the specification clearly describes increased permeability in response to K_{Ca} or K_{ATP} agonists in abnormal microvasculature, but not in normal microvasculature. (E.g., Specification, Figures 1A and 1B; and at page 18, line 12 through page 19, line 9).

Further, all of the cited references and the general knowledge in the art failed to teach that the relative quantity of potassium channels in abnormal microvasculature is greater compared to the quantity in normal microvasculature. This feature contributes to the successful functioning of the claimed method of delivering a medicant to an abnormal brain region in a mammalian

subject. It is only the present specification that provides this knowledge (e.g., at page 8, lines 6-10; and in Example 2, at page 19, lines 10-20).

Therefore, minus the hindsight provided by the disclosures of the present specification, success would not have been reasonably expected for the claimed method of delivering a medicant to an abnormal brain region in a mammalian subject, employing potassium channel agonists. Given this, the successful utility of the pharmaceutical compositions and kits (Claims 97-109) would also not have been reasonably expected based on the cited Black, Sobey *et al.*, and Cherksey references.

Consequently, Applicant respectfully requests the Examiner to withdraw the rejection of Claims 1-34 and 97-109 on this ground.

A.2. Rejection of Claims 108 and 109 under 35 U.S.C. § 103(a)

Examiner Nikodem had stated that ". . . [w]ith regard to a kit-the lack of instructions does not render a kit as non-obvious. It would have been obvious to anyone of skill in the art to add an instruction manual to a method that is being marketed commercially." (Office Action, Item 9).

Because, the claimed method of delivering a medicant to an abnormal brain region in a mammalian subject is non-obvious (as explained above), the instructions for using the potassium channel agonist to practice the method would also not have been obvious, minus the hindsight provided by Applicant's specification.

In numerous cases, including *In re Gulack*, 217 USPQ 401, 403 (CCPA 1983); *In re Lowry*, 32 USPQ2d 1031, 1033 (Fed. Cir. 1994), and *ex parte Carver*, 227 USPQ 465, 469 (BPAI 1985), the legal principal is well established that "printed matter may well constitute structural limitations upon which patentability can be predicated," in condideration of *all* the claim limitations taken as a whole. (*In re Gulack*, 217 USPQ, at 403, end of footnote 8).

In addition, the Examiner Clark suggested during the interview that an amendment of Claim 108 to recite "by increasing the permeability of a capillary or arteriole delivering blood to

cells of the abnormal brain region," would make the claim allowable. Applicant has so amended Claim 108.

Therefore, Applicant respectfully requests the Examiner to withdraw the rejection of Claims 108-109 on this ground.

B. Rejection of Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34 under the Doctrine of Obviousness Type Double Patenting

The Examiner rejected Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34 under the Doctrine of Obviousness Type Double Patenting over Claims 1-6 of Black (U.S. Patent No. 5,434,137), in view of Sobey *et al.* (Stroke 28[11]:2290-4 [1997]) and Cherksey (U.S. Patent No. 5,234,947).

During the telephonic interview, Examiner Clark stated that if Claims 1-34 and 108-109 were not obvious, then this double patenting rejection would also be overcome.

Applicant believes that Applicant's arguments presented above show that the combination of the cited Black, Sobey et al., and Cherksey references fails to make obvious the invention claimed in Claims 1-5, 7-9, 11; 12, 14-22, 24-26, and 28-34, because these three cited references failed to make obvious any of Claims 1-34.

Therefore, the rejection based on the doctrine of obviousness type double patenting is improper, and Applicant respectfully requests it be withdrawn.

C. Rejection of Claims 1-34, and 97-109 under 35 U.S.C. § 112, first paragraph

Examiner Nikodem asserted that " the specification fails to teach any treatment or show any treatment effect of any disease, disease state or pathology," and that "the art of drug delivery and eliciting a treatment effect is an unpredictable art." (Office Action, Item 15). In support of his argument, the examiner cited Sabaté et al. for the proposition that "the blood-brain barrier prevents access to the brain of numerous macromolecules of therapeutic value." (Office Action, Item 15). Thus, while asserting that there are macromolecules of therapeutic

value, the examiner simultaneously asserted that "it is unpredictable in the art as to what pharmaceutical compositions actually will have a therapeutic effect, in vivo," and that it would require undue experimentation to identify and test all pharmaceutical compositions for an effect. (Office Action, Item 16).

Examiner Nikodem seems to have missed the articulated goal of the invention, especially overcoming the blood-brain barrier so that known therapeutic molecules can penetrate to abnormal brain regions (e.g., Specification, at page 7, lines 3-7). The specification is directed to the use of medicants conventionally used to treat brain abnormalities, for example at page 3, lines 10-25; page 13, line 1 through page 14, line 23, where classes of known chemotherapeutic agents and conventional methods for their delivery are exemplified. In particular, the specification states that "the amount of medicant that is employed is within a conventional dose range for each medicant," although the dose is potentially lower as a benefit of the invention, implying that the medicants are already known to the skilled artisan. (Specification, at page 14, lines 10-11).

Therefore, it is well within the knowledge of the skilled artisan to select a known medicant, such as a chemotherapeutic agent or macromolecule (e.g., specification, at page 13, line 1 through page 14, line 23), for delivery to an abnormal brain region using the claimed methods, compositions and kits. (As mentioned hereinabove, Applicant has deleted from the Markush groups of Claims 6, 23, and 101, the recitation of "DNA expression vector", "viral vector", "oligonucleotide", and "nucleotide analog" and has placed them in new Claims 110-112.)

Consequently, Applicant respectfully requests the Examiner withdraw the rejection of Claims 1-34 and 108-109 on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would

expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,
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